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09/766,161	01/19/2001	Michael S. Colman	MCA-538	9144

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Kevin S. Lemack
Nields & Lemack
Suite 8
176 E. Main Street
Westboro, MA 01581

EXAMINER	
MENON, KRISHNAN S	

ART UNIT	PAPER NUMBER
1723	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

AS

Office Action Summary	Application No.	Applicant(s)	
	09/766,161	COLMAN, MICHAEL S.	
	Examiner	Art Unit	
	Krishnan S Menon	1723	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13 and 17-19 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 13 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussey et al (US 6,011,148) in view of Geiger et al (US 5,589,342).

Claims 17-19: Since this is a Jepson claim, the applicant is admitting that 'the fractionation of linear nucleic acids contained in a liquid sample by ultrafiltration' is prior art. Bussey teaches a process of ultrafiltration of nucleic acids (abstract, col 5 lines 3-6), using differential pressure as a driving force (col 7 lines 30-45), from a liquid sample by diluting the sample (col 7 lines 44-55) in order to retain pure nucleic acids as in claim 17. The diluent comprises water, Tris-HCl, EDTA etc as in claim 19 (col 11 lines 50-65, col 10 lines 5-15).

Bussey does not teach fractionation of DNA fragments, and expresses the retention of the nucleic acids in terms of molecular weights instead of base pairs as in claims 17 and 18. The instant application only describes the process of purifying DNA fragments using ultrafiltration with increased recovery by dilution of the sample, even though the application recites the process as "fractionation" (see page 2 para 2 and 3,

page 3 para 1 and 2, last 2 lines of page 4, para 3 of page 6, etc.). Bussey uses the same method of dilution, similar ultrafiltration membranes (compare the membrane – col 6 lines 24-54), and the same differential pressure as in the instant application, and therefore, it would be obvious to one of ordinary skill in the art at the time of invention that the process taught by Bussey also would provide the same recovery of the nucleic acid fragments as in the instant application.

Re claim 13, while Bussey teaches all the limitations of claim 13, as explained in the forgoing paragraphs, Bussey does not specifically state the use of a first and then a second pressure. However, Bussey teaches that "Generally filtration process is faster with higher pressures, but higher pressures are likely to cause shearing of the nucleic acid or loss due to passage through the membrane" (lines 30-40, col 7). Therefore, it is obvious for one of ordinary skill in the art at the time of the invention that the flow of DNA fragments through an ultrafiltration membrane is pressure dependent and one could subject the samples to different pressures to obtain different flow rates of each species. It is also obvious to one ordinarily skilled in the art at the time of invention that filtering a second time with a different pressure would result in better recovery as taught by Bussey, because lower trans-membrane pressures would afford recovery of lower nucleic acid fragments (col 7 lines 30-40).

Re the limitation "consisting essentially of linear nucleic acids" in the instant claims, Bussey does not state the nucleic acids being linear. However, according to Geiger, "...both single-stranded and double-stranded nucleic acids are commonly believed to be linear polymers ... " (col 7 lines 17-21). Busy col 3 lines 1-10 teaches

the preferred embodiment as having DNA, particularly plasmid DNA. From this statement it would be obvious to one of ordinary skill in the art at the time of invention that Bussey does not preclude linear DNA.

2. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bussey (148) in view of WO 00/66723 and Geiger '342.

Claim 1: Bussey teaches a process of ultrafiltration of nucleic acids (abstract, col 5 lines 3-6), using differential pressure as a driving force (col 7 lines 30-45), from a liquid sample by diluting the sample (col 7 lines 44-55) in order to retain pure nucleic acids as in claim 17. Bussey does not teach fractionation, fragment length, and diluting to dryness. The instant application only describes the process of purifying DNA fragments using ultrafiltration with increased recovery by dilution of the sample, even though the application recites the process as "fractionation" (see page 2 para 2 and 3, page 3 para 1 and 2, last 2 lines of page 4, para 3 of page 6, etc.). Bussey uses the same method of dilution, the same differential pressure as in the instant application, and similar ultrafiltration membrane, and therefore, it would be obvious to one of ordinary skill in the art at the time of invention that the process taught by Bussey also would provide the same recovery of the nucleic acid fragments as in the instant application. Re filtration to dryness, WO-723 teaches ultrafiltration to dryness of nucleic acid samples with membranes. It would be obvious to one of ordinary skill in the art at the time of invention to use the teaching of WO-723 in the teaching of Bussey to filter the

sample to dryness to handle multiple samples in one step with multi-well filters (see WO 723 abstract).

Claim 2: The dilution is encompassed (col 7 lines 44-55) of Bussey's teachings of diafiltration and continuous diafiltration.

Claim 3: Bussey teaches the diluents water, EDTA , Tris-HCl, and their mixtures (lines 5-20 of col 10, and lines 45-55 of col 11.)

Claim 4: Teaches separating the double stranded DNA or RNA (col 3, lines 24-32), when he states that the concentration of the single stranded DNA is less than 1%.

Claim 5: the pressure differential (trans-membrane pressure) is constant (Lines 28-32, col. 7)

Claim 6, 7 and 8 adds further limitations over claim 1: In addition to the recovery of nucleic acids with ultrafiltration membranes at constant pressure differential (see above), the pressures 25" Hg and 10" Hg fall within the range taught by Bussey. The ultrafiltration membrane has upstream (feed) and downstream (permeate) sides (col 7 lines 25-45).

Re the newly added limitation "consisting essentially of linear nucleic acids" in the instant claims, Bussey does not state the nucleic acids being linear. However, according to Geiger, "...both single-stranded and double-stranded nucleic acids are commonly believed to be linear polymers ... " (col 7 lines 17-21). It would be obvious to one of ordinary skill in the art at the time of invention that the DNA Bussey teaches also would be linear.

3. Claims 9-12 rejected under 35 U.S.C. 103(a) as being unpatentable over Bussey (148) in view of Simon (us 5,434,048) and Geiger '342.

Bussey (148) discloses a process for "fractionation" of contaminants by adding to said sample monovalent cations (col 10, lines 5-20) and contacting said sample with an ultrafiltration membrane and subjecting a pressure differential to the sample as discussed above. Bussey does not teach the use of condensing agents like bivalent cations as recited by claims 9 and 10. Simon (048) teaches the use of monovalent and bivalent cations, i.e., KCl and MgCl2 (examples I and II) for removal of contaminants by ultrafiltration (col 3 lines 14-17). It would be obvious to one ordinarily skilled in the art at the time of invention to use Simon's teachings of using bivalent cations with Bussey's teachings of removal of contaminants from the sample using an ultrafiltration membrane under a pressure differential for asymmetric amplification as taught by Simon (col 4 lines14-17).

Claims 11 and 12 add further limitations of monovalent cations (claim 11) and constant pressure differential (claim 12) (see Bussey: example I; col 7 lines 29-44)

Re the newly added limitation "consisting essentially of linear nucleic acids" in the instant claims, Bussey does not state the nucleic acids being linear. However, according to Geiger, "...both single-stranded and double-stranded nucleic acids are commonly believed to be linear polymers ... " (col 7 lines 17-21). It would be obvious to one of ordinary skill in the art at the time of invention that the DNA Bussey teaches also would be linear.

Response to Amendment

The Declaration under 37 CFR 1.132 filed 2/17/04 is insufficient to overcome the rejection of instant claims based upon 35 USC 103 (a) as set forth in the last Office action because:

The declaration only provides arguments against the rejection of the instant claims without providing any evidence to overcome the rejection and make the claims allowable.

In page 6, Dr. Leonard argues that Bussey ref teaches only circular plasmid DNA. However, in line 1, col 3 of the ref, Bussey teaches that preferred nucleic acid is DNA, particularly, plasmid DNA, which would not preclude linear DNA. In col 4 line 66 – col 5 line 15, Bussey teaches a whole list of nucleic acids including several kinds of DNA and DNA fragments, many of which are not circular.

On the same page, Dr Leonard argues that Bussey teaches dilution for the purpose of salt contaminant removal, not for improved recovery of DNA fragments as the applicant claims. In response, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

On page 7 starting at the third line, Dr. Leonard points out that the tangential flow filtration would cause the salt concentration to change dramatically over the course of the filtration, and thereby undermine the basis of enhanced separation and recovery. This argument seems to be contradictory to the statement that the reason for Bussey to

dilute is to remove salt contaminant. In the examiner's understanding of ultrafiltration process, the low molecular weight salt components dissolved in the solution would readily pass through the membrane ***without*** generating a concentration gradient of the salts between the retentate side and the permeate side of the membrane. Such a concentration gradient would be generated only by the components that get filtered by the membrane. This would be true for both tangential and dead-end filtration. Therefore, how would the salt concentration dramatically change in tangential flow ultrafiltration? On the other hand, if the salt concentration were to change during ultrafiltration, wouldn't that change be more dramatic in the dead-end filtration the applicant purports than in the tangential flow filtration? Also please note that Claims 9-13 and 17-19 do not have any limitations to indicate that the process is not tangential flow filtration, and this argument is not commensurate in scope to those claims.

Dr. Leonard's argument on "consisting essentially of linear nucleic acids" also implies that there is only nucleic acid in the solution, and contaminants are not present, or at least not present in an amount that would alter the characteristics of the sample. Again, this argument also seems to be contradictory: Applicants clearly state that the need for dilution is to change the characteristic of the DNA, that is, increase their radius of gyration (specification page 4) by desalting the phosphate backbone. In pages 1 and 2 of the specification discusses ultrafiltration process for separation of PCR products from contaminating reaction components. Page 3, first paragraph discloses dilution before ultrafiltration for the improved recovery of smaller PCR products. These disclosures appear to the examiner as a process for recovering DNA fragments from a

PCR which contains contaminants like reaction components and salts, contrary to the statement of Dr. Leonard, which seems to say that the solution is pure and contains only DNA fragments and the invention is to fractionate the DNA into fragments of different sizes.

Response to Arguments

Applicant's arguments filed 7/28/03 have been fully considered but they are not persuasive.

Most of the arguments by the applicant have been addressed in the response to amendment/declaration above. Arguments against the use of TFF (Tangential Flow Filtration) in laboratory scale filtration is not commensurate in scope to the claims because laboratory scale filtration is not claimed, nor there is a limitation as to the limitation on volume hold-up. Such limitations are also not normally patentable: *In re Rose* , 220 F.2d 459, 105 USPQ 237 (CCPA 1955) (Claims directed to a lumber package "of appreciable size and weight requiring handling by a lift truck" where held unpatentable over prior art lumber packages which could be lifted by hand because limitations relating to the size of the package were not sufficient to patentably distinguish over the prior art.); In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) ("mere scaling up of a prior art process capable of being scaled up, if such were the case, would not establish patentability in a claim to an old process so scaled." 531 F.2d at 1053, 189 USPQ at 148.). *In Gardner v. TEC Systems, Inc.,* 725 F.2d 1338, 220 USPQ 777 (Fed. Cir. 1984), cert. denied, 469 U.S. 830, 225 USPQ 232 (1984), the

Federal Circuit held that, where the only difference between the prior art and the claims was a recitation of relative dimensions of the claimed device and a device having the claimed relative dimensions would not perform differently than the prior art device, the claimed device was not patentably distinct from the prior

Argument that TFF cannot run to dryness: Examiner agrees that TFF process cannot run to dryness. However, filtration to dryness is not a limitation in all the claims, but only some of the claims and the rejection of those claims have a supporting reference (ref WO 00/66723) that teaches ultrafiltration to dryness. Bussey teaches ultrafiltration of DNA after dilution as pointed out in the rejection. Bussey also teaches repeated dilution, and use of dead-end filtration in the subsequent paragraphs in col 7 and 8 and in the examples. Also please note that by the Jepson claim 17, Applicant concedes that the invention is diluting the sample to increase the recovery smaller fragments (of 300 base pairs or less), and fractionation of nucleic acids by ultrafiltration is known in the art.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued

examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Krishnan S Menon whose telephone number is 571-272-1143. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Wanda L Walker can be reached on 571-272-1151. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Krishnan Menon
Patent Examiner

W. L. WALKER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1700